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(54) Title: PHARMACEUTICAL COMPOSITIONS OF AZITHROMYCIN

(57) Abstract: A pharmaceutical composition for oral administration, comprising azithromycin in the form of a monohydrate as a pharmaceutically active ingredient, a sweetener, a flavourant, a buffer, optionally a filler, and optionally a thickener.

**Pharmaceutical compositions of azithromycin**

The present invention relates to organic compounds, such as azithromycin. Azithromycin is a pharmaceutically active compound, e.g. useful as an antibacterial agent, see e.g. The Merck Index, 12th edition, Item 946.

We have found a pharmaceutical composition comprising azithromycin in the form of a monohydrate from which azithromycin may be released appropriately and in which azithromycin in the form of a monohydrate is not converted into azithromycin in the form of a dihydrate upon reconsitiution in an aqueous liquid.

In one aspect the present invention provides a pharmaceutical composition for oral administration, comprising, e.g. consisting of

- azithromycin in the form of a (stable) monohydrate as a pharmaceutically active ingredient,
- a sweetener,
- a flavourant,
- a buffer,
- optionally a filler, and
  optionally a thickener.

Azithromycin in the form of a (stable) monohydrate and its preparation is e.g. disclosed in WO0100640, EP0984020 (azithromycin in the form of a monohydrate isopropanol clathrate) and WO 0210181, and includes azithromycin in the form of a (stable) monohydrate as claimed in WO0100640, EP0984020 and WO 0210181,

Per gram of azithromycin in the form of a monohydrate preferably

- 12.50 to 22.50 gram of a sweetener,
- 0.05 to 0.5 gram of a flavourant,
- 0.05 to 0.5 gram of a buffer
- 0.00 to 0.5 gram of a filler and
- 0.00 to 1.0 gram of a thickener are present.

A sweetener includes sugars and arteficial sweeteners. A sugar includes one or more sugars, such as saccharose; and an arteficial sweetener includes one or more arteficial sweeteners, such as aspartame. A preferred sweetener includes a sugar and a mixture of a

sugar and an artificial sweetener. A sweetener more preferably includes a sugar and optionally an arteficial sweetener in a weight ratio of sugar : arteficial sweetener from 1:0 to 44:1.

A flavourant includes one or more flavourants, e.g. such as flavourants which are commercially available, for example, e.g. selected from the group consisting of, Antiamarum (Flavopharm), Toffee (Silesia) and flavourants available from Firmenich, e.g. Vanilla Cream, Apricot, Golden Syrup, Strawberry, Pinapple, Blackcurrant, Caramel Golden Syrup, Raspberry, Apricot Durarome, Tropical Fruit, Red Fruit. Flavourant combinations e.g. include Antiamarum+Redfruit, Antiamarum+Toffee, Vanilla Cream+Pinapple, Vanilla Cream+Apricot, Vanilla Cream+Raspberry, preferably Antiamarum (Flavopharm)+Toffee (Silesia), Vanilla Cream+Apricot (both Firmenich).

A buffer includes a single buffer substance or a mixture of buffer substances, such as buffers as conventional, preferably Tri-Na-phosphate.

A filler includes one or more fillers, e.g. fillers as conventional, preferably $SiO_2$, such as Aerosil(s)®.

A thickener includes one or more thickeners, e.g. thickeners as conventional, preferably selected from the group consisting of methylcelluloses, e.g. Methylcellulose A4C®., Methocel E3 Premium®, Methocel K 100 M Premium EP®; hydroxypropylcelluloses, e.g. Klucel LF®, carboxymethylcelluloses, e.g. sodium carboxymethylcelluloses, such as Nycel ZSC®, polyvinylpyrrolidones, e.g. Kollidon 90®, natural and artificial gums, e.g. xantham gum; preferably xantham gum+hydroxypropylcellulose.

A composition according to the present invention may be prepared as appropriate, e.g. according to a method as conventional, such as mixing the ingredients to obtain a homogenous composition.

A composition according to the present invention is useful as a suspension powder/granulate, i.e. a powder/granulate which, when reconstituted in a liquid, forms a suspension or emulsion for oral administration. A liquid includes an aqueous liquid, e.g. water.

In another aspect the present invention provides a suspension or emulsion obtainable by mixing a pharmaceutical composition according to the present invention with an aqueous liquid, e.g. water.

In another aspect the present invention provides a pharmaceutical unit dosage form comprising sachets containing a pharmaceutical composition according to the present invention wherein each sachet contains 100 mg, 200 mg or 300 mg, preferably 200 mg, of azithromycin in the form of a monohydrate.

In a suspension or emulsion according to the present invention azithromycin in the form of a monohydrate may be surprisingly not converted into azithromycin in the form of a dihydrate, even at evelated temperatures, e.g. at 40°C, although it is known that azothromycin in aqueous liquid has a great tendency to form the dihydrate rather than the monohydrate. For determination whether azithromycin is in the form of a monohydrate or in the form of a dihydrate which may be carried out by X-ray diffraction pattern determination, drying of the azithromycin obtained from a suspension sample should be gentle. E.g. a suspension for oral administration obtained by reconstitution of a pharmaceutical composition according to the present invention in an aqueous liquid may be subjected to centrifugation, azithromycin obtained may be filtrated off, gently dried e.g. at or slightly above room temperature and the dried powder obtained may be subjected to X-ray diffraction pattern determination.

In the following examples all temperatures are in Centigrade and are uncorrected.

**Example**

1.2 g of azithromycin in the form of a monohydrate are mixed with 22.05 g of saccharose powder, 0.04 g xantham gum, 0.04 g of hydroxypropylcellulose (Klucel®), 0.256 g of tri-Na-phosphate, 0.024 g of Siliciumdioxid (Aerosil®); 0.18 g of aspartame and 0.12 g of a flavourant.

As a flavourant Antiamarum (Flavipharm) + Toffeee (Silesia) or Vanilla Cream (Firmenich)+Apricot (Firmenich) are used.

The homogenous mixture obtained is divided into 6 equal portionsand each portion is filled into a separate sachet. 6 sachets containing a suspension granulate for oral administration comprising each 200 mg of azithromycin in the form a monohydrate are obtained.

The suspension granulate obtained is reconstituted in water and a suspension is obtained. A part of the suspension is warmed up to 40°.

From both suspensions azithromycin is isolated and subjected to X-ray diffraction pattern determination. Azithromycin isolated from both suspension (warmed and unwarmed) is found to be in the form of azithromycin in the form of a monohydrate (and not in the form of a dihydrate).

**Patent claims**

1. Pharmaceutical composition for oral administration, comprising
   - azithromycin in the form of a monohydrate as a pharmaceutically active ingredient,
   - a sweetener,
   - a flavourant,
   - a buffer,
   - optionally a filler, and
   - optionally a thickener.

2. A pharmaceutical composition according to claim 1 comprising per gram of azithromycin in the form of a monohydrate,
   - 12.50 to 22.50 gram of a sweetener,
   - 0.05 to 0.5 gram of a flavourant,
   - 0.05 to 0.5 gram of a buffer
   - 0.00 to 0.5 gram of a filler and
   - 0.00 to 1.0 gram of a thickener.

3. A pharmaceutical composition according to any one of claims 1 or 2, comprising azithromycin in the form of a monohydrate, saccharose, aspartame, a flavourant, tri-Na-phosphate, siliciumdioxide, xantham gum and hydroxypropylcellulose.

4. A pharmaceutical composition according to any one of claims 1 or 2, comprising per gram of azithromycin in the form of a monohydrate 15 to 20 g of saccharose, 0.08 to 0.2 g of aspartame, 0.08 to 0.2 g of a flavourant, 0.1 to 0.3 g of tri-Na-phosphate, 0.01 to 0.1 g of siliciumdioxide, 0.02 to 0.04 g of xantham gum and 0.02 to 0.04 g of hydroxypropylcellulose.

5. A pharmaceutical composition according to any one of claims 1 to 4 which is a suspension powder/granulate.

6. A pharmaceutical unit dosage form comprising sachets containing a pharmaceutical composition according to any one of claims 1 to 5 wherein each sachet contains 200 mg of azithromycin in the form of a monohydrate.

7. A suspension or emulsion obtainable by mixing a pharmaceutical composition according to any one of claims 5 or 6 with an aqueous liquid.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06489

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H17/08 A61K31/7048 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Beranová, P |

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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PCT/EP 03/06489

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